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Review Article

Portal hypertension: from pathophysiology to clinical practice

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Abstract: Portal hypertension (PHT) is responsible for the more severe and often lethal complications of cirrhosis such as bleeding oesophageal varices, ascites, renal dysfunction and hepatic encephalopathy. Because of the combined impact of these complications, PHT remains the most important cause of morbidity and mortality in patients with cirrhosis. Over the years, it has become clear that a decrease in portal pressure is not only protective against the risk of variceal (re)bleeding but is also associated with a lower long-term risk of developing complications and an improved long-term survival. A milestone in therapy was the introduction of non-selective β-blockers for the prevention of bleeding and rebleeding of gastro-esophageal varices. However, in practice, less than half the patients under β-blockade are protected from these risks, supporting the overall demand for innovation and expansion of our therapeutic armamentarium. Recent advances in the knowledge of the pathophysiology of cirrhotic PHT have directed future therapy towards the increased intrahepatic vascular resistance, which, in part, is determined by an increased hepatic vascular tone. This increased vasculogenic component provides the rationale for the potential use of therapies aimed at increasing intrahepatic vasorelaxing capacity via gene therapy, liver-selective nitric oxide donors and statines on the one hand, and at antagonizing excessive intrahepatic vasoconstrictor force through the use of endothelin antagonists, angiotensin blockers, α_1 adrenergic antagonists or combined α_1- and non-selective β-blockers or somatostatin analogues on the other. The focus of this review is to give an update on the pathophysiology of PHT in order to elucidate these potential novel strategies subsequently.

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Portal hypertension (PHT) is characterized by an increase in portal vein pressure as a result of impediment to portal flow (1). Depending on the level of impediment, PHT is classified as either prehepatic, intrahepatic or posthepatic. Intrahepatic PHT is most often caused by cirrhosis, either alcoholic in origin or because of chronic HBV or HCV infection, and affects over 90% of patients with PHT in Europe and the USA (1). Taking into account the high prevalence of HCV worldwide and the emergence of non-alcoholic fatty liver disease, the incidence of intrahepatic PHT is not expected to decrease in the next decennium (2).

An innovating and challenging concept that has received considerable attention over the last few years is that PHT, in order for it to become clinically relevant, should increase above a critical threshold. The use of an invasive technique to measure the hepatic venous pressure gradient (HVPG), which reflects the gradient between the portal vein and vena cava pressure, has played a major role in the construct of this concept and has therefore become indispensable at least in clinical trials for PHT (1, 3, 4). It is now generally agreed that the HVPG should increase above a threshold of 12 mmHg for complications of PHT, such as ruptured oesophageal varices and ascites, to occur (5–7). Several clinical–haemodynamic correlations have supported the principle of a critical threshold as longitudinal studies have demonstrated a decrease in variceal size and an increased survival when the portal pressure gradient could be reduced below this threshold (8, 9), or when a reduction in HVPG of at least 20% of the baseline values could be obtained (9–12).

Furthermore, it was recently shown that achieving these goals not only protected against risk of variceal rebleeding but also markedly reduced the long-term risk of developing other complications of PHT (hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome), and improved survival over an 8-year follow-up period after the index variceal bleeding (13). Therefore, these targets have now become the therapeutic aims in the treatment of PHT.

The available armamentarium to do so is far from satisfactory. Since its introduction more than 20 years ago by Lebrec et al. (14) for the prevention of variceal rebleeding, and a few years later by Pascal and Cales (15) for primary prophylaxis, non-selective β-blockers have remained the cornerstone in the treatment for PHT (16, 17). However, a long-term decrease in portal pressure is achieved only in 30–40% of patients (9), whereas an additionally estimated 10–20% of patients discontinue β-blockers because of intolerance (18, 19). As a consequence, the search for potential new strategies is emerging and is linked to the growing interest in the pathophysiology of PHT.

The present review aims to provide an update on the pathophysiology of PHT and to elucidate the different proposed novel strategies starting from this background.

Pathophysiological basis of PHT

According to Ohm's law ($\Delta P = Q \times R$), changes in portal venous pressure are proportional to alterations in blood flow and resistance. In the normal liver, intrahepatic resistance changes with variations in portal blood flow, thereby keeping portal pressure within normal limits. In cirrhosis, however, both intrahepatic resistance and splanchnic blood flow are increased (19, 20). The initiating factor is an increase in intrahepatic vascular resistance (IHVR), whereas the increase in splanchnic blood flow is a secondary phenomenon that maintains or worsens the increased portal pressure and gives rise to the hyperdynamic systemic state, characterized by an increased heart rate, cardiac output, plasma volume and a low overall vascular resistance (19) (Fig. 1).

Increased intrahepatic vascular tone: cellular and humoral components

The increased IHVR is a consequence of an alteration in the hepatic microcirculation, which has long been thought of to be 'fixed' and as such non-modifiable, because of fibrosis, thrombosis, nodule formation and collagenization ('capillarization') of the space of Disse (Fig. 2A and B). The pioneering work by Bhathal and Grossman (21) demonstrated that the increased IHVR in an isolated perfused cirrhotic rat liver could be reduced by vasodilators. They estimated that this active, dynamic modifiable component of IHVR accounted for 30% of the total IHVR, and suggested, as a basis for their findings, that an increased number of a special type of *contractile cells* in a strategic location within the cirrhotic nodule may modulate, through contraction, the

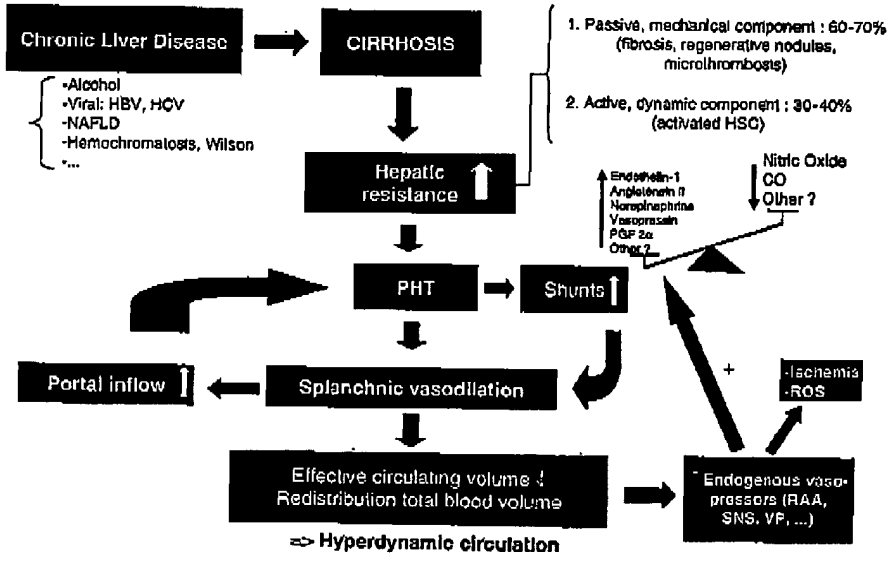

Fig. 1. Schematic representation of the pathophysiology of portal hypertension. HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; HSC, hepatic stellate cells; PHT, portal hypertension; RAA, renin-angiotensin-aldosterone; SNS, sympathetic nervous system; VP, vasopressin; ROS, radical oxygen species.

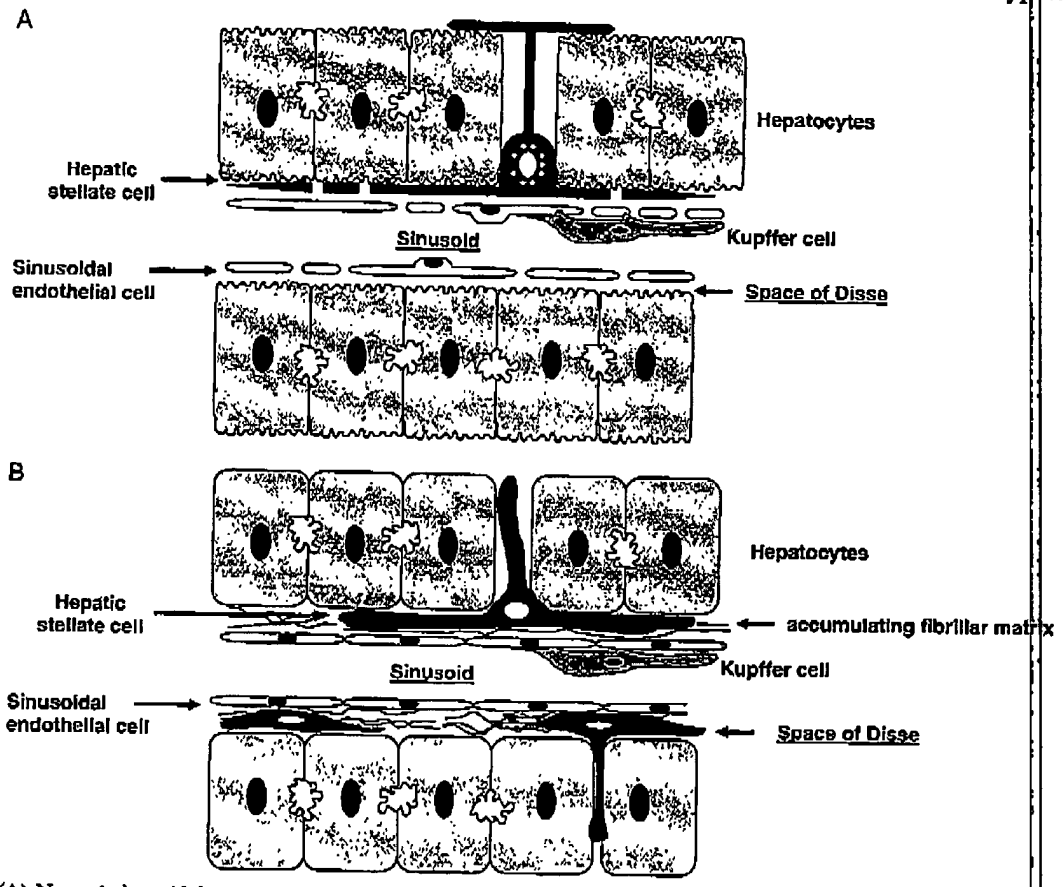

Fig. 2. (A) Normal sinusoidal architecture. (B) Sinusoidal architecture during liver injury: 'capillarization' of the space of Disse: stellate cells proliferate and are surrounded by accumulating fibrillar matrix; hepatocytes are deprived of microvilli and endothelial fenestrae become closed.

resistance of the hepatic vascular bed to portal inflow. This hypothesis induced the search for contractile elements within the liver and for abnormalities in the mechanisms regulating cell contraction. Although other cellular elements such as the vascular smooth muscle cells of the intrahepatic vasculature (i.e. small portal venules in portal areas) may also be involved, many studies have pointed out a dominant role for the activated hepatic stellate cells (HSCs) and/or the hepatic portal and interface myofibroblast (19, 22–24). To date, it is not yet clear whether different cell populations are present or whether it concerns different phenotypic configurations of a similar cell type (25). It is clear, however, that as a result of liver cell injury, perisinusoidal HSCs undergo a striking morphological and functional transition to a 'myofibroblast-like' phenotype with increased fibrogenetic, contractile, immunomodulatory and migratory potential (26). Because of their location around the sinusoid and the expression of smooth muscle-like proteins, activated HSCs by contraction reduce the calibre of the sinusoid (23, 27). Therefore, a resemblance to pericytes, a cell type with smooth muscle features that is thought to regulate blood flow via pericapillary constriction, has been suggested (22). Portal myofibroblasts and interface myofibroblasts reside, respectively, in the fibrous septa and the portal tracts and at the interface between liver parenchyma and fibrotic septa. Both may contribute by compressing the venous channels and shunts that are present within these septa.

An additional feature in the active IHVR is the imbalance in vasoactive substances. In cirrhosis, there is an overexpression locally and/or systemically of (neuro)humoral *vasoconstrictors*, such as norepinephrine (NE), endothelins (ETs), angiotensin-II (AT-II) and leukotrienes, leading to an increased vascular tone of the cirrhotic liver as well as to an exaggerated response ('hyper-responsiveness') of the hepatic vascular bed to some of these mediators (28, 29). Of these vasoconstrictors, ET-1 seems the most potent one. Both hepatic concentration and ET receptor expression are increased in human and experimental cirrhosis

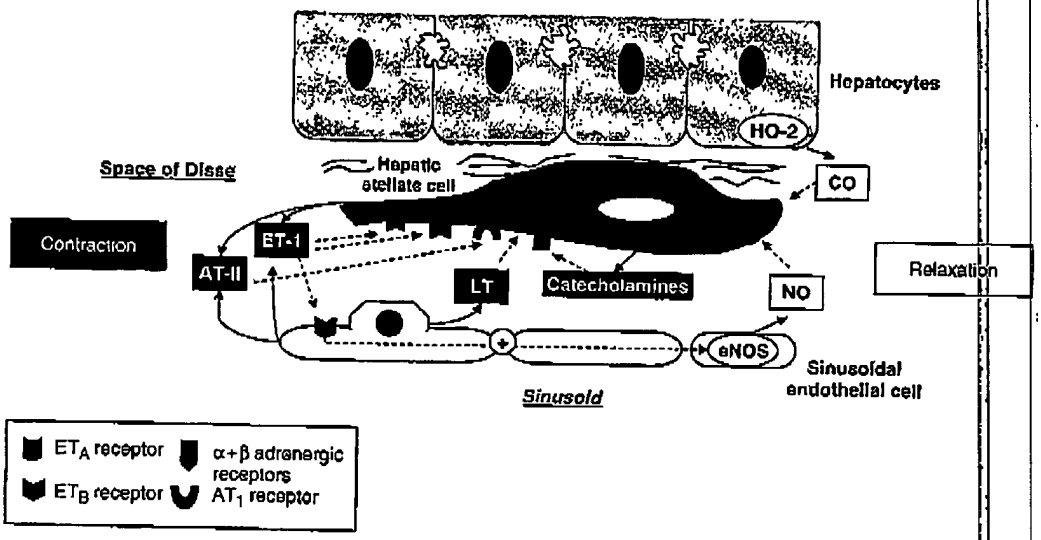

Fig. 3. Modulation of contraction/relaxation of activated HSC. ET-1, endothelin-1; AT-II, angiotensin-II; CO, carbon monoxide; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; HO-2, haeme-oxygenase-2; LT, leukotrienes.

(30). The ET_A-receptor subtype, present on vascular contractile cells, causes vasoconstriction, while the ET_B-receptor subtype on endothelial cells is believed to cause vasorelaxation by stimulating endothelial nitric oxide synthase (eNOS) (28) (Fig. 3). Furthermore, ET-1 has also been reported to induce a strong pro-fibrogenetic response, emphasizing its role not only in the active dynamic but also in the 'passive' intrahepatic resistance (31, 32).

A second major player is AT-II. Arroyo et al. (33) showed that the renin–angiotensin–aldosterone system (RAAS) was implicated in the regulation of portal blood flow. Recently, Bataller et al. (34) described that stellate cells express the AT-1 receptor, which leads to contraction and proliferation. Additionally, as is the case with ET-1, an autocrine source of AT-II became apparent, indicating that stellate cells harbour all the components for local signalling in response to AT-II (35) (Fig. 3). Bataller et al. (36) also documented that AT-II is a fibrogenic cytokine through the generation of radical oxygen species by NADPH oxidase stimulation, as inhibition of NADPH oxidase of the AT-1 receptor attenuated liver injury and fibrosis.

A third factor is the influence of the adrenergic neurohumoral system. Oben et al. (37) tested the hypothesis that HSC respond to and produce sympathetic nervous system neurotransmitters. In cultured HSC and intact mice with liver injury, it was shown that HSCs expressed adrenoceptors and catecholamine biosynthetic enzymes and that they released NE. In Dbh(−/−) mice, which lack dopamine β-hydroxylase, the liver injury-related fibrogenic responses were inhibited, suggesting an important role for neurohumoral factors (Fig. 3).

In contrast to the intrahepatic excess in vasoconstrictive potential, the intrahepatic production and/or availability of *vasodilators* remains insufficient. NO, the most well-known vasodilator substance, is a reactive, gaseous molecule with a half-life of 3–5 s, produced from L-arginine by one of the three NOS isoforms. These isoforms are categorized into two families of enzymes: endothelial cells (eNOS) and neurons (nNOS) contain a distinct 'constitutive' NOS, whereas a wide variety of cells, mainly cells involved in inflammatory reactions, are capable of expressing the inducible form (iNOS). In the liver, both eNOS and iNOS can be active. In chronic liver injury, the molecular basis of the intrahepatic NO deficiency has uniformly been attributed to a decreased activity of the endothelial isoform (eNOS) (38–41) (Fig. 3). Whether this dysfunction is because of diminished translation or complex posttranslational modifications (such as the impaired serine–threonine kinase Akt activation of eNOS and/or increased interaction of eNOS with the inhibitory protein caveolin-1) remains currently under discussion (38–40). Besides a decreased production, there might also be an increased degradation of NO (by formation of peroxynitrite) because of enhanced superoxide activity as a result of superoxide dismutase deficiency, leading to diminished bioavailability of NO (42) (Fig. 4).

In addition to NO, attention has recently been drawn to carbon monoxide, CO. Similar to NO, CO is a gaseous molecule with the capacity to

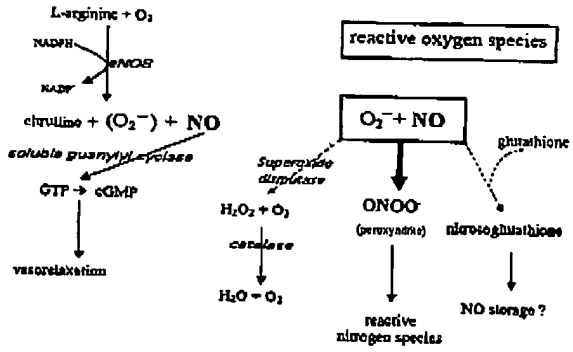

Fig. 4. Proposed scheme of nitric oxide (NO) and superoxide signalling, adapted from (41). NO is a potent vasodilator acting through activation of soluble guanylyl cyclase in vasoactive effector cells. Superoxide is able to react with NO to form reactive nitrogen species, which do not have vasodilatory effects. Increased superoxide levels, as a result of decreased superoxide dismutase activity, can therefore lead to increased peroxynitrite formation, as such reducing NO bioavailability. Glutathione and NO may lead to possible storage of NO derivatives.

relax smooth muscle cells through the activation of soluble guanylate cyclase. It was therefore suggested that CO could also participate in the regulation of intrahepatic blood flow (43). Intrahepatic CO stems from the degration of haeme by haeme-oxygenase (HO), leading to biliverdin and CO. Two HO isoforms have been characterized: HO-1, which is inducible by a variety of stressors such as hypothermia, cytokines, ischaemia, etc., and HO-2, which is thought to constitute the major enzyme activity in the liver parenchyma (44). Recently, a second constitutive isoform has been found, HO-3, which is nearly devoid of catalytic activity and functions chiefly as a haeme-sensing or a haeme-binding protein (45). In normal liver, the topographic hepatic distribution of these different isoforms is distinctly different (46). Whereas HO-1 is observed only in Kuppfer cells, HO-2 is present in parenchymal cells but not in Kuppfer cells. Goda et al. (46) have documented that CO evoked by HO-2 in the parenchymal cells and released in the space of Disse serves as the physiological relaxant of hepatic sinusoids in the healthy liver, while HO-1 is haemodynamically of no importance (Fig. 3). It must, however, be realized that CO is a far less potent mediator compared with NO as the ability of CO to activate soluble guanylate is approximately 50 times weaker than NO (47). The specific role of CO in the increased IHVR associated with cirrhosis remains to be investigated.

Splanchnic hyperaemia and arterial vasodilation

The second contributing factor to PHT is an increased blood flow in the portal venous system. This is because of splanchnic arteriolar vasodilatation (48, 49). The increase in blood flow is responsible for the maintenance and further aggravation of the portal hypertensive syndrome in conditions of increased IHVR, for high portal venous inflow *per se* is not sufficient to induce PHT in the face of a healthy compliant liver (50). High portal inflow also explains why PHT persists despite the presence of an extensive collateral network that may divert up to 80% of the portal blood flow (48). The splanchnic arteriolar vasodilation is because of increased levels of circulating vasodilator substances and reduced sensitivity ('hyporesponsiveness') to vasoconstrictors (49). Early studies mainly focused on the role of circulating vasodilator substances of splanchnic origin such as glucagon, vasoactive intestinal peptide, bile salts, platelet-activating factor, substance P, calcitonin gene-related peptide, atrial natriuretic peptide, etc. (51), because these agents accumulate in chronic liver disease as a result of reduced hepatic metabolism and/or increased portosystemic shunting (52). The strongest evidence concerns *glucagon*, whereas for other substances controversy still exists (52–56). Elevated plasma glucagon levels are present in cirrhotic patients and in portal hypertensive rat models, and a partial decrease of the splanchnic hyperaemia has been obtained by infusion of glucagon antibodies or of somatostatin in portal hypertensive rats (57–60). Splanchnic hyperaemia was also obtained when glucagon levels were increased in healthy rats to values found in cirrhotic rats (58). Hyperglucagonaemia would account for 30–40% of the splanchnic vasodilation in the chronic portal hypertensive state (58). These data clearly support a pathogenetic role for glucagon, and favour the use of somatostatin in the treatment of variceal haemorrhage.

Paracrine vasoactive substances produced by the splanchnic vascular endothelium, such as *NO* and *prostacyclin*, are also implicated in the pathogenesis of the portal hypertensive syndrome, as inhibition of respectively NO and prostanoid synthesis as well as removal of the endothelium, corrects, in large part, splanchnic and systemic haemodynamics in portal hypertensive rats (49, 61). Moreover, crosstalk exists between both pathways (61). For the excess of NO in the splanchnic and systemic circulation, it has been previously assumed that the inducible isoform of NOS (iNOS) was responsible. This was based on the hypothesis of Vallance and Moncada (62), who proposed that endotoxaemia, sometimes present in cirrhosis, induces expression of iNOS in vessel walls. However, this hypothesis could not be validated because iNOS was not

significantly upregulated in the splanchnic and systemic vasculature of cirrhotic animals and because dexamethasone, known to inhibit iNOS expression, did not prevent the hyperdynamic circulation to develop (63, 64). The major enzymatic source of the vascular NO overproduction was shown to be eNOS (63–66). An important role in the upregulation of eNOS in this context has been attributed to chronic increases in shear stress stimulation in endothelial cells as a result of the increased portal tributary blood flow and the hyperdynamic circulation (67–69). The pathogenetic relationship between shear stress and arterial vasodilation was further reinforced by the observation that long-term β-blockade in partial portal vein-ligated rats corrected arterial hyporeactivity to vasoconstrictors and systemic eNOS overexpression, suggesting possible mechanisms of action of β-blockade either indirectly by decreasing cardiac output by β_1 receptors or through a direct vascular β_2 effect (67). In addition to shear stress, several other factors, such as vascular endothelial growth factor (70, 71) and pro-inflammatory cytokines (72) have also been associated with enhanced systemic eNOS activity. Of particular interest is the work by Wiest et al. (72), who have shown that tumour necrosis factor-α (TNF-α), a pro-inflammatory cytokine, was induced in mesenteric lymph nodes by bacterial translocation and accumulated in the serum. This TNF-α production was associated with elevated levels of tetrahydrobiopterin (BH_4), a TNF-α-stimulated co-factor and enhancer of eNOS-derived NO biosynthesis in mesenteric vasculature, and establishes a link between pro-inflammatory cytokines and eNOS-derived NO production in the absence of inducible NOS.

In addition to NO, CO was also suggested to participate in the mesenteric vascular hyporesponsiveness of portal hypertensive rats (73).

These pathophysiological insights form the basis to use vasoconstrictors such as vasopressin, somatostatin and non-selective adrenergic β-blockers in the treatment of PHT.

The hyperdynamic circulation

In a more advanced phase, patients with cirrhosis and PHT exhibit a typical 'hyperdynamic' circulation with increased cardiac output, heart rate and plasmavolume and decreased arterial blood pressure and systemic vascular resistance (74). These haemodynamic changes are initially induced by splanchnic and later on by peripheral vasodilatation, leading to reduced systemic vascular resistance and an abnormal distribution of the blood volume with a reduced central or 'effective' blood volume as key elements. The basis for this phenomenon is thought to originate either from the presence of excess circulating vasodilators that escape hepatic degradation or bypass the liver through portosystemic shunting, or from increased shear stress in the systemic circulation, as discussed above (67–69, 75). The low arterial pressure and central hypovolaemia lead to the activation of several counter-regulatory systems, such as the RAAS, the *sympathetic* nervous system and the non-osmotic release of arginine vasopressin, in an attempt to maintain a stable perfusion pressure by means of vasoconstriction and sodium and water retention. The above-mentioned 'hyporesponsiveness' of the splanchnic vascular wall to vasoconstrictor agents explains why the hyperdynamic circulation increases with progression of the disease despite increasing activation of these homeostatic vasoconstrictor systems (74). Furthermore, persistent activation of these systems appears to worsen the active component of intrahepatic resistance and promotes vasoconstriction with ischaemia and subsequent formation of oxidative stress in essential end organs. This complex interplay between enhanced vasodilatation in one vascular territory and vasoconstriction in another, plays a central role in the development of the multiorgan disturbance in cirrhosis (76). This diversity in vascular reactions within one cirrhotic patient may either be owing to locally increasing levels of endogenous vasoconstrictors compared with the vasodilators, relative 'underfilling' of the vasodilated systemic circulation or a change in vascular reactivity (74, 75). The presence and severity of the hyperdynamic circulation in patients with cirrhosis may significantly affect the patient's prognosis on a short-term basis. Several studies have already emphasized the relation between the degree of arterial hypotension in cirrhosis and the severity of hepatic dysfunction, hepatic decompensation and survival (77, 78).

Future potential strategies in the treatment of PHT

Based on the pathophysiology, several (theoretical) pharmacological strategies can be proposed (Table 1). Ideally, a drug should decrease IHVR while maintaining or enhancing hepatic blood flow. Furthermore, the vasodilatory effect of this drug should be limited to the hepatic microcirculation to prevent a worsening in splanchnic/systemic vasodilatation. If this drug could additionally also be capable of decreasing hepatic fibrosis and improving liver function, this drug would be invaluable in clinical practice.

Table 1. Pharmacostrategies in portal hypertension

1. Aiming to decrease increased intrahepatic resistance:
   Active, dynamic resistance
   1. Increase intrahepatic NO bioavailability
      a. Currently used: isosorbide-5-mononitrate and dinitrate, nitroglycerin
      b. Future potential strategies:
         Gene transfer with eNOS or co-factor Akt
         Statins
         Selective hepatic NO delivery: V-Pyrro-NO, NO-ursodeoxycholic acid, etc.
         Decrease intrahepatic NO-degradation to $ONOO^-$ by increasing anti-oxidans capacity
   2. Increase intrahepatic CO (?)
   3. Antagonize effect of excess of intrahepatic vasoconstrictive substances
      a. Endothelin-1 antagonism
         Bosentan
         Newly developed ET-blockers: Tezosentan ?
      b. Angiotensin-II
         Selective AT-II-blockers: Losartan, etc.
      c. Adrenergic antagonists
         Prazosin (α-1-blocker)
         Carvedilol (combined α-1- and non-selective β-blocker)
      d. Somatostatin-receptor-1 analogues
   Passive resistance modulation: anti-fibrotic drugs (?)
2. Aiming to decrease splanchnic hyperaemia
      a. Non-selective β-blockers
      b. Vasopressin and its analogues
      c. Somatostatin and somatostatin analogues
         Sustained-release preparations for chronic use?

Decrease the increased IHVR

Selective increase of intrahepatic NO

As the intrahepatic NO deficiency has been attributed to a decreased activity of eNOS, substitution of the deficient enzyme or another isoform would seem the next logic step. Both the endothelial and neuronal NOS isoforms were transfected to cirrhotic rats using gene transfer (38, 79). This resulted in increased NO synthesis and lowered portal pressure without systemic haemodynamic side effects (38, 79). However, because of the transient expression when using an adenoviral vector and potential safety hazards such as the potential hepatotoxicity and the immunogenic character of currently used viral vectors in humans, this approach does not yet seem applicable clinically (80). Nevertheless, this approach not only clearly proves the major haemodynamic role of eNOS in the pathogenesis of PHT but it also provides 'proof of principle' that therapeutic strategies aimed at increasing intrahepatic NO content are useful. A similar rationale resulted in successful gene transfer with Akt, which is a deficient intrahepatic co-factor of eNOS (40).

A next strategy is to increase intrahepatic NO by the use of *statins*. Besides lowering lipids, statins are known to increase Akt activity and thus NOS activity. This has proven to be correct in a recent pilot study in which simvastatin was able to enhance hepatic NO production and decrease hepatic sinusoidal resistance, as well as attenuate the postprandial increase in portal pressure in cirrhotic patients (81). Additionally, statins might have a direct inhibitory effect on HSC contraction, presumably by decreasing oxidative stress and by decreasing the intermediate isoprenoids such as farnesylpyrophosphate and geranylgeranylpyrophosphate. Isoprenoids are lipid attachments involved in the posttranslational modification of numerous proteins, among others, the γ unit of heterotrimeric G-protein of Rho, which is involved in pro-contractile signal transduction in the HSC (82).

Finally, new *liver-specific NO donors* are under investigation. A first hepato-selective NO donor, V-pyrro/NO, was reported to decrease portal pressure in a portal hypertensive animal model (83). However, questions have arisen concerning its liver selectivity (49). A next promising molecule is an NO-releasing derivative of ursodeoxycholic acid. However, insufficient data are available at present to draw firm conclusions (84–86).

Another rationale is to prevent degradation of intrahepatic NO to peroxynitrite by superoxide by *increasing the anti-oxidans capacity* (42). Haemodynamic studies in anaesthetized rats with extrahepatic PHT showed that chronic administration of *N*-acetylcysteine, a pro-drug of glutathione, prevented the development of the portal hypertensive syndrome (87). The same authors extended their findings to a cirrhotic rat model of PHT by administrating lipoic acid, a thiol-containing antioxidant with additional iron-chelating and lipid peroxidation-inhibiting properties, and found that in biliary cirrhotic rats the development of the hyperdynamic circulation could also be prevented (88). Furthermore, this was associated with a decreased synthesis of systemic NO. These findings, however, have not been confirmed in humans.

Antagonize intrahepatic vasoconstrictors

Antagonizing ET-1 also seems a reasonable strategy. From a pharmacological point of view, *ET_A antagonists* and *ET_B agonists* would be the molecules of choice. However, in contrast to accepted thinking, ET_B stimulation with the pure ET_B agonist sarafotoxin caused a greater increase in portal pressure in cirrhotic rats than in control rats (89). Further studies with mixed ET_A–ET_B antagonists resulted in incompatible results: bosentan decreased portal pressure (90, 91), whereas a second-generation mixed antagonist RO 48-5695 did not affect PHT and even worsened liver fibrosis (92). Selective ET_A antagonists, such as

LU 135252 and FR 139317, also led to conflicting data (89, 93). More studies are clearly needed. A further concern has been the observation that treatment with ET antagonists for pulmonary hypertension led to liver impairment in 10% of patients treated (94). New ET blockers with less hepatic side effects are announced.

A further step in decreasing vasoconstrictive hyperactivity in the injured liver is the use of *angiotensin blockade*. Activation of the RAAS is a frequent finding in patients with cirrhosis, especially in those with more advanced disease where the levels of AT-II correlate with the degree of systemic arteriolar dilation and with sodium retention (51, 76–78). Studies with angiotensin-converting enzyme (ACE) inhibitors in the 1980s, although resulting in lowered HVPG, were discouraging because of a marked decrease in the mean arterial pressure and a subsequent further worsening of the hyperdynamic circulation (33). The reasons why ACE inhibitors are less successful in the treatment of PHT are thought to be threefold (95). Firstly, there seems to be a genetic polymorphism in ACE and AT-II, leading to large differences in different studies. Secondly, AT-II returns to basal levels during chronic inhibition probably by local generation of AT-II under the influence of chymases. Thirdly, chronic ACE inhibition might lead to increased endothelial NO and PGE_2/PGI_2 release. However, the documentation of the expression of AT-1 receptor on HSCs by Bataller et al. (34), together with the development of selective AT-II-receptor blockers, renewed the interest in the approach to inhibit the RAAS. In a non-randomized study in portal hypertensive patients, losartan, a typical AT-II-receptor blocker, caused a marked reduction in portal pressure with minimal systemic hypotension and adverse events (96). Unfortunately, these remarkable findings were not confirmed in subsequent randomized-controlled trials, in which AT-II blockade with irbesartan or losartan had only a slight or no effect on portal pressure, while it decreased the arterial pressure and the glomerular filtration rate (97–99). These agents are therefore dangerous in advanced cirrhosis, but may still have a role in preventing the progression of hepatic fibrosis in early stages of the disease (100).

A third approach in this context would be to induce adrenergic antagonism, either by means of an *α_1-adrenergic antagonist* or a *combined α- and β-blocker*. Prazosin, an α_1-adrenergic antagonist, was shown to markedly reduce the IHVR in treated cirrhotic patients not only by a reduction in HVPG but also by an increase in hepatic blood flow (101). However, the lack of liver selectivity resulted in a significant reduction in arterial pressure and systemic vascular resistance. This in turn led to a further activation of endogenous vasoactive systems, with plasma volume expansion, sodium retention and in some cases, accumulation of ascites (102). These findings discouraged its use as monotherapy in the treatment of PHT. Interestingly enough, these adverse effects could be attenuated by the combined administration of prazosin with propranolol (102). This latter approach showed even more effectiveness in reducing HVPG than the association of propranolol plus ISMN (103). This drug combination therefore needs further assessment in randomized-controlled trials.

Carvedilol combines non-selective β-blocking properties with α_1-antagonistic properties. Other effects, although not fully defined, are calcium channel antagonism at high dosages and antioxidant effects (104). Carvedilol is two- to fourfold more potent than propanolol in its β-blocking profile and has less α_1-antagonist activity than prazosin (105). Given this unique pharmacologic profile, the potential exists for carvedilol to reduce PHT by decreasing the IHVR via its α_1-antagonist acitivity as well as by decreasing splanchnic hyperaemia through its non-selective β-blocking properties. Trials assessing the effect on portal pressure resulted in a mean reduction of HVPG of 16–43% after single and multiple doses (104). When compared with propanolol, equal or enhanced efficacy in lowering HVPG was observed. However, the proportion of patients developing symptomatic hypotension was significantly higher in patients treated with carvedilol, especially in patients with Child–Pugh B or C cirrhosis. It was suggested that the efficacy and adverse effects of carvedilol could be dose related (105). Therefore, multiple-dose trials comparing carvedilol with propanolol are needed to fully recognize the role of carvedilol in the treatment of PHT.

A fourth proposal might be the use of *somatostatin analogues*. Somatostatin has earned its place in the treatment of acute variceal bleeding by its ability to reduce portal pressure by reducing splanchnic hyperaemia and gastro-oesophageal collateral blood flow (106). The bases of these effects on the splanchnic circulation are attributed to the capacity of somatostatin to inhibit glucagon and other gastrointestinal vasodilatory peptides, but a direct action on vascular smooth muscle has also been proposed (107). Recently, five somatostatin receptors have been cloned, termed SSTR1 to SSTR5 (107, 108). Information regarding the distribution of these SSTRs is scarce but a predominant expression of SSTR2 seems to be present in pancreatic islets and presumably also in the splanchnic arteriolar

system. This would explain the effect of somatostatin on the splanchnic flow via, on the one hand, SSTR2-mediated glucagon suppression, and a potentiation of protein kinase C-dependent vasoconstrictors on mesenteric vascular smooth muscle cells on the other (109). With regard to intrahepatic effects, it was observed that somatostatin is able to increase hepatic vagal nerve activity with hepatic sinusoidal dilatation as a result (110). Additionally, Reynaert et al. (108) showed that rat HSCs express SSTR subtypes 1–3 and that preincubation with somatostatin was able to inhibit ET-1-induced HSC contraction via activation of SSTR1. This provides the prospect of lowering the increased IHVR via selective stimulation of the SSTR1 receptor.

Decrease splanchnic blood flow

Minor progress has been made in treating splanchnic hyperaemia and the hyperdynamic circulation. Non-selective β-blockers, terlipressin and somatostatin, have been used for this purpose, but the latter two can only be given parenterally and on a short-term basis, leaving us with β-blockers as the sole usable drug on a long-term basis (111). The development of sustained-release preparations for chronic use is awaited, but long-acting somatostatine derivatives did not prove to be very helpful (109). The effort to block the pathogenetic excessive NO release in the systemic and splanchnic circulation, showed, experimentally (112, 113) as well as in human studies (114), that the hyperdynamic circulation and splanchnic hyperaemia could be attenuated but without a decrease in portal pressure, suggesting that an increase of intrahepatic resistance was produced at the same time. The latter originates presumably from a further aggravation of the intrahepatic NO deficiency because of a generalized effect on NOS.

Summary and perspectives

Complications of PHT are responsible for disabling morbidity and mortality in patients with cirrhosis. Decreasing portal pressure has therefore become a major target in treating these patients. Currently, therapy will at least temporarily remain limited to the use of these β-blockers because of the lack of valuable alternatives. The main concern of these drugs, however, is the fact that only half of the patients achieve the preset haemodynamic goals and the potential further impairment of liver function because of decrease in total the hepatic flow. Therefore, expansion in the knowledge of the pathophysiology of PHT is urgently needed as this might provide new and useful strategies for the future. Currently, some of these new pharmacostrategies have already reached the clinic and are being currently tested for efficacy and tolerance. The main drawback at present, however, is the lack of (hepato)selectivity, which is needed because of the paradoxal haemodynamic ntra- and extrahepatic characteristics.

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References

1. Wongcharatrawee S, Groszmann R J. Diagnosing portal hypertension. Baillieres Best Pract Res Clin Gastroenterol 2000; 14: 881–94.
2. Ramesh S, Sanyal A J. Hepatitis C and nonalcoholic fatty liver disease. Semin Liv Dis 2004; 24: 399–413.
3. Myers J D, Taylor W J. An estimation of portal venous pressure by occlusive catherization of a hepatic venule. J Clin Invest 1951; 30: 662–3.
4. Groszmann R J, Wongcharatwee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology 2003; 39: 280–2.
5. Garcia-Tsao G, Groszmann R J, Fisher R L, Conn H O, Atterbury C E, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 1985; 5: 419–24.
6. Casado M, Bosch J, Garcia-Pagan J C, Bru C, Banares R, Bandi J C, et al. Clinical events after transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings. Gastroenterology 1998; 114: 1296–303.
7. Vorobioff J, Groszmann R J, Picabea E, Gamen M, Villavicencio R, Bordato J, et al. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: a 10-year prospective study. Gastroenterology 1996; 11: 701–9.
8. Groszmann R J, Bosch J, Grace N D, Conn H O, Garcia-Tsao G, Navasa M, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. Gastroenterology 1990; 90: 1401–7.
9. Feu F, Garcia-Pagan J C, Bosch J, Luca A, Teres J, Escorsell A, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995; 346: 1056–9.
10. Escorsell A, Bordas J M, Castaneda B, Llach J, Garcia-Pagan J C, Rodes J, et al. Predictive value of the variceal pressure response to continued pharmacological therapy in patients with cirrhosis and portal hypertension. Hepatology 2000; 31: 1061–7.
11. Merkel C, Bolognesi M, Sacerdoti D, Bombonato G, Bellini D, Bighin R, et al. The hemodynamic response to medical treatment of portal hypertension as a predictor of clinical effectiveness in the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology 2000; 32: 930–4.
12. Villanueva C, Balanzo J, Novella M T, Soriano G, Sainz S, Torras X, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the therapy for

prevention of variceal rebleeding. N Engl J Med 1996; 334: 1624–9.
13. Abraldes J G, Tarantino I, Turnes J, Garcia-Pagan J C, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003; 37: 902–8.
14. Lebrec D, Poynard T, Hillon P, Benhamou J P. Propanolol for the prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. N Engl J Med 1981; 305: 1371–4.
15. Pascal J P, Cales P. Propanolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. N Engl J Med 1987; 317: 856–61.
16. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology 1995; 22: 332–54.
17. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. Semin Liv Dis 1999; 19: 475–505.
18. Villeneuve J P, Pomier-Layrargues G, Infante-Rivard C, Willems B, Huet P M, Marleau D, et al. Propanolol for the prevention of recurrent variceal rebleeding in cirrhosis: a controlled trial. Hepatology 1986; 6: 1239–43.
19. Bosch J, Garcia-Pagan J C. Complications of cirrhosis. I. Portal hypertension. J Hepatol 2000; 32(Suppl. 1): 141–56.
20. Bosch J, Groszmann RJ, eds. Portal Hypertension: Pathophysiology and Treatment. Oxford: Blackwell, 1994.
21. Bhathal P S, Grossman H J. Reduction of the increased intrahepatic vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. J Hepatol 1985; 1: 325–37.
22. Pinzani M, Failli P, Ruocco C, Casini A, Milani S, Baldi E, et al. Fat-storing cells as liver-specific pericytes. Spatial dynamics of agonist-stimulated intracellular calcium transients. J Clin Invest 1992; 90: 642–6.
23. Kawada N, Tran-Thi T A, Klein H, Decker K. The contraction of hepatic stellate (Ito) cells stimulated with vasoactive substances. Possible involvement of endothelin-1 and nitric oxide in the regulation of the sinusoidal tonus. Eur J Biochem 1993; 213: 815–23.
24. Rockey D C, Housset C N, Friedman S L. Activation-dependent contractility of rat hepatic lipocytes in culture and in vivo. J Clin Invest 1993; 92: 1795–804.
25. Cassiman D, Roskams T. Beauty is in the eye of the beholder: emerging concepts and pitfalls in hepatic stellate cell research. J Hepatol 2002; 37: 527–35.
26. Friedman S L. Seminars in medicine of the Beth Israel Hospital, Boston. The cellular basis of hepatic fibrosis. Mechanisms and treatment strategies. N Engl J Med 1993; 328: 1828–35.
27. Zhang J X, Pegoli W J, Clemens M G. Endothelin-1 induces direct constriction of the hepatic sinusoids. Am J Physiol 1994; 266: G624–32.
28. Rockey D C. Vascular mediators in the injured liver. Hepatology 2003; 37: 4–12.
29. Graupera M, Garcia-Pagan J C, Titos E, Claria J, Massaguer A, Bosch J, et al. 5-lipoxygenase inhibition reduces intrahepatic vascular resistance of cirrhotic rat livers: a possible role of cysteinyl-leukotrienes. Gastroenterology 2002; 122: 387–93.
30. Ghandi C R, Sproat L A, Subbotin V M. Increased hepatic endothelin-1 levels and endothelin receptor density in cirrhotic rats. Life Sci 1996; 58: 55–62.
31. Rockey D C, Chung J J. Endothelin antagonism in experimental hepatic fibrosis. Implications for endothelin in the pathogenesis of wound healing. J Clin Invest 1996; 98: 1381–8.
32. Cho J J, Hocher B, Herbst H, Jia J D, Ruehl M, Hahn E G, et al. An oral endothelin-A receptor antagonist blocks collagen synthesis and deposition in advanced rat liver fibrosis. Gastroenterology 2000; 118: 1169–78.
33. Arroyo V, Bosch J, Mauri M, Ribera F, Navarro-Lopez F, Rodes J. Effect of angiotensin-II blockade on systemic and hepatic hemodynamics and on the renin–angiotensin–aldosterone system in cirrhosis with ascites. Eur J Clin Invest 1981; 11: 221–9.
34. Bataller R, Gines P, Nicolas J M, Gorbig M N, Garcia-Ramallo E, Gasull X, et al. Angiotensin induces contraction and proliferation of human hepatic stellate cells. Gastroenterology 2000; 118: 1149–56.
35. Bataller R, Gines P, Lora J, Sole M, Nicolas J M, Jimenez W. Evidence for a local renin-angiotensin system in human liver: expression in activated hepatic stellate cells. Hepatology 2001; 34: 399A.
36. Bataller R, Schwabe R F, Choi Y H, Yang L, Paik Y H, Lindquist J, et al. NADPH oxidase signal transduces angiotensin II in hepatic stellate cells and is critical in hepatic fibrosis. J Clin Invest 2003; 112: 1383–94.
37. Oben J A, Roskams T, Yang S, Lin H, Sinelli N, Torbenson M, et al. Hepatic fibrogenesis requires sympathetic neurotransmitters. Gut 2004; 53: 438–45.
38. Van de Casteele M, Omasta A, Janssens S, Roskams T, Desmet V, Nevens F, et al. In vivo gene transfer of endothelial nitric oxide synthase decreases portal pressure in anaesthetised carbon tetrachloride cirrhotic rats. Gut 2002; 51: 440–5.
39. Shah V J, Toruner M, Haddad F, Cadelina G, Papapetropoulos A, Chido K, et al. Impaired endothelial nitric oxide synthase activity associated with enhanced caveolin binding in experimental cirrhosis in the rat. Gastroenterology 1999; 117: 1222–8.
40. Moralez-Ruiz M, Cejudo-Martin P, Fernandez-Varo G, Tugues S, Ros J, Angeli P, et al. Transduction of the liver with activated Akt normalizes portal pressure in cirrhotic rats. Gastroenterology 2003; 125: 522–31.
41. Rockey D C, Chung J J. Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial dysfunction in portal hypertension. Gastroenterology 1998; 114: 344–51.
42. Van de Casteele M, Van Pelt J F, Nevens F, Fevery J, Reichen J. Low NO bioavailability in CCl4 cirrhotic rat livers might result from low NO synthesis combined with decreased superoxide dismutase activity allowing superoxide-mediated NO breakdown: a comparison of two portal hypertensive rat models with healthy controls. Comp Hepatol 2003; 2: 2.
43. Suematsu M, Goda N, Sano T, Kashiwaga S, Egawa T, Shinoda Y, et al. Carbon monoxide: an endogenous modulator of sinusoidal tone in the perfused rat liver. J Clin Invest 1995; 96: 2431–6.
44. Maines M D. Heme oxygenase: function, multiplicity, regulation mechanism and clinical applications. FASEB J 1988; 2: 2557–68.
45. McCoubrey W K Jr., Huang T J, Maines M D. Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase-3. Eur J Biochem 1997; 247: 725–32.
46. Goda N, Suzuki K, Naito M, Takeoka S, Tsuchida E, Ishimura Y, et al. Distribution of heme oxygenase isoforms in rat liver. Topographic basis of carbon monoxide-mediated microvascular relaxation. J Clin Invest 1998; 101: 604–12.

47. Suematsu M, Wakabayashi Y, Ishimura Y. Gaseous monoxides: a new class of microvascular regulator in the liver. Cardiovas Res 1996; 32: 679–86.
48. Vorobioff J, Bredfeldt J, Groszmann R J. Hyperdynamic circulation in a portal hypertensive rat model: a primary factor for the maintenance of chronic portal hypertension. Am J Physiol 1983; 244: G52–6.
49. Wiest R, Groszmann R J. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. Hepatology 2002; 35: 478–91.
50. Sikuler E, Groszmann R J. Interaction of flow and resistance in maintenace of portal hypertension in a rat model. Am J Physiol 1986; 250: G205–12.
51. Möller S, Bendtsen F, Henriksen J H. Vasoactive substances in the circulatory dysfunction of cirrhosis. Scand J Clin Lab Invest 2001; 61: 421–30.
52. Benoit J N, Barrowman J A, Harper S L, Kvietys P R, Granger D N. Role of humoral factors in the intestinal hyperemia associated with chronic portal hypertension. Am J Physiol 1984; 247: E486–93.
53. Genecin P, Polio J, Colombato L A, Ferraioli G, Reuben A, Groszmann R J. Role of bile acids do not mediate the hyperdynamic circulation in portal hypertensive rats. Am J Physiol 1990; 259: G21–5.
54. Thomas S H, Joh T, Benoit J N. Role of bile acids in splanchnic hemodynamic response to chronic portal hypertensive rats. Dig Dis Sci 1991; 36: 1243–8.
55. Fernandez M, Casadevall M, Schuligoi R, Pizcueta P, Panes J, Barrachina M D, et al. Neonatal capsaicin treatment does not prevent splanchnic vasodilation in portal hypertensive rats. Hepatology 1994; 20: 1609–14.
56. Lee S S, Sharkey K A. Capsaicin treatment blocks development of hyperkinetic circulation in portal hypertensive rats. Am J Physiol 1993; 264: G868–73.
57. Gomis R, Fernandez-Alvarez J, Pizcueta P, Fernandez M, Casamitjana R, Bosch J, et al. Impaired function of pancreatic islets from rats with portal hypertension resulting from cirrhosis and partial vein ligation. Hepatology 1994; 19: 1257–61.
58. Silva G, Navasa M, Bosch J, Chesta J, Pilar Pizcueta M, Casamitjana R, et al. Hemodynamic effects of glucagon in portal hypertension. Hepatology 1990; 11: 668–73.
59. Kravetz D, Bosch J, Arderiu M T, Pizcueta M P, Casamitjana R, Rivera F, et al. Effects of somatostatin on splanchnic hemodynamics and plasma glucagons in portal hypertensive rats. Am J Physiol 1988; 254: G322–5.
60. Benoit J N, Zimmerman B, Premen A J, Go V L, Granger D N. Role of glucagons in splanchnic hyperemia of chronic portal hypertension. Am J Physiol 1986; 251: G674–8.
61. Fernandez M, Garcia-Pagan J C, Casadevall M, Mourelle M I, Pique J M, Bosch J, et al. Acute and chronic cyclooxygenase blockade in portal hypertensive rats: influence on nitric oxide biosynthesis. Gastroenterology 1996; 110: 1529–35.
62. Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? Lancet 1991; 1: 776.
63. Martin P, Xu D, Niederberger M, Weigert A, Tsai P, St John J, et al. Upregulation of endothelial constitutive NOS: a major role in the increased NO production in cirrhotic rats. Am J Physiol 1996; 270: F494–9.
64. Fernandez M, Garcia-Pagan J C, Casadevall M, Bernadich C, Piera C, Whittle B J, et al. Evidence against a role for inducible nitric oxide synthase in the hyperdynamic circulation of portal hypertensive rats. Gastroenterology 1995; 108: 1487–95.
65. Wiest R, Shah V J, Sessa W, Groszmann R J. Nitric oxide overproduction by eNOS precedes the hyperdynamic circulation in portal hypertensive rats. Am J Physiol 1999; 276: G1043–51.
66. Cahill P A, Redmond E M, Hodges R, Zhang S, Sitzmann J V. Increased endothelial nitric oxide synthase activity in the hyperaemic vessels of portal hypertensive rats. J Hepatol 1996; 25: 370–8.
67. Pateron D, Tazi K A, Sogni P, Heller J, Chagneau C, Poirel O, et al. Role of aortic nitric oxide synthase 3 (eNOS) in the systemic vasodilation of portal hypertension. Gastroenterology 2000; 119: 1996–2000.
68. Braillon A, Lee S, Girod C, Peignoux-Martinot M, Valla D, Lebrec D. Role of portosystemic shunts in the hyperkinetic circulation of the portal hypertensive rat. J Lab Clin Med 1986; 108: 543–8.
69. Tazi K A, Barriere B, Moreau R, Heller J, Sogni P, Pateron D, et al. Role of shear stress in aortic eNOS upregulation in rats with biliary cirrhosis. Gastroenterology 2002; 122: 1869–77.
70. Akiyoshi F, Sata M, Suzuki H, Uchimura Y, Mitsuyama K, Matsuo K, et al. Serum vascular endothelial growth factor levels in various liver diseases. Dig Dis Sci 1998; 43: 41–5.
71. Bouloumie A, Schini-Kerth V B, Busse R. Vascular endothelial growth factour up-regulates nitric oxide synthase expression in endothelial cells. Cardiovasc Res 1999; 41: 509–10.
72. Wiest R, Das S, Cadelina G, Garcia-Tsao G, Milstien S, Groszmann R J. Bacterial translocation in cirrhotic rats stimulates eNOS-derived NO production and impairs mesenteric vascular contractility. J Clin Invest 1999; 104: 1223–33.
73. Fernandez M, Lambrecht R W, Bonkovsky H. Increased heme oxygenase activity in splanchnic organs from portal hypertensive rats: role in modulating mesenteric vascular reactivity. J Hepatol 2001; 34: 812–7.
74. Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: an overview. Pharm Ther 2001; 89: 221–31.
75. Henriksen J H, Kizska-Kanowitz M, Bendtsen F. Review article: volume expansion in patients with cirrhosis. Aliment Pharmacol Ther 2002; 16: 12–23.
76. Arroyo V, Jimenez W. Complications of cirrhosis. II. Renal and circulatory dysfunction. Light and shadows in an important clinical problem. J Hepatol 2000; 32: 157–70.
77. Llach J, Gines P, Arroyo V, Rimola A, Tito L, Badalamenti S, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988; 94: 482–7.
78. Fernandez-Esparrach G, Sanchez-Fueyo A, Gines P, Uriz J, Quinto L, Ventura P J, et al. A prognostic model for predicting survival in cirrhosis with ascites. J Hepatol 2001; 34: 46–52.
79. Yu Q, Shao R, Qian H S, George S E, Rockey D C. Gene transfer of the neuronal NO synthase isoform to cirrhotic rat liver amcliorates portal hypertension. J Clin Invest 2000; 105: 741–8.
80. Rockey D C. Cellular pathophysiology of portal hypertension and prospects for management with gene therapy. Clin Liv Dis 2001; 5: 851–65.
81. Zafra C, Abraldes J G, Turnes J, Berzigotti A, Fernandez M, Garcia-Pagan J C, et al. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis. Gastroenterology 2004; 126: 749–55.
82. Yanase M, Ikeda H, Matsui A, Noiri E, Tomiya T, Arai M, et al. HMG-COA reductase inhibitor modulates

collagen gel-contraction by hepatic myofibroblast-like stellate cell line: involvement of geranylgeranylated proteins. Comp Hepatol 2004; 3: S21.
83. Moal F, Vuillemin E, Wang J, Veal N, Oberti F, Cales P. Chronic antifibrotic and hemodynamic effects of a new liver specific NO donor (V-pyrro/NO) in bile duct ligated rats. Hepatology 2001; 32: 186A.
84. Fiorucci S, Antonelli E, Morelli O, Mencabelli A, Casini A, Mello T, et al. NCX-1000, a NO-releasing derivative of ursodeoxycholic acid, selectively delivers NO to the live rand protects against development of portal hypertension. Proc Natl Acad Sci USA 2001; 98: 8897–902.
85. Fiorucci S, Antonelli E, Brancaleone V, Sanpaolo L, Orlandi S, Distributti E, et al. NCX-1000, a nitric oxide releasing derivative of ursodeoxycholic acid, ameliorates portal hypertension and lowers norepinephrine-induced intrahepatic resistance in the isolated and perfused rat liver. J Hepatol 2003; 39: 932–9.
86. Loureira-Silva M R, Cadelina G W, Iwakiri Y, Groszmann R J. A liver-specific nitric oxide donor improves the intrahepatic vascular response to both portal blood flow increase and methoxamine in cirrhotic rats. J Hepatol 2003; 39: 940–6.
87. Fernando B, Marley R, Holt S, Anand R, Harry D, Sanderson P, et al. *N*-acetylcysteine prevents development of the hyperdynamic circulation in the portal hypertensive rat. Hepatology 1998; 28: 689–94.
88. Marley R, Holt S, Fernando B, Harry D, Anand R, Goodier D, et al. Lipoic acid prevents the development of the hyperdynamic circulation in anesthetized rats with biliary cirrhosis. Hepatology 1999; 29: 1358–63.
89. Kojima H, Sakurai S, Kuriyama S, Yoshiji H, Imazu H, Uemura M, et al. Endothelin-1 plays a major role in portal hypertension of biliary cirrhotic rats through endothelin receptor subtype B togheter with subtype A in vivo. J Hepatol 2001; 34: 805–11.
90. Reichen J, Gerbes A L, Steiner M J, Sagesser H, Clozel M. The effect of endothelin and its agonist bosentan on hemodynamics and microvascular exchange in cirrhotic rat liver. J Hepatol 1998; 28: 1020–30.
91. Sogni P, Moreau R, Gomola A, Gadano A, Cailmail S, Calmus Y, et al. Beneficial effects of bosentan, a mixed ET(A) and ET(B) receptor antagonist, in portal hypertensive rats. Hepatology 1998; 28: 655–9.
92. Poo J L, Jiménez W, Maria M R, Bosch-Marce M, Bordas N, Morales-Ruiz M, et al. Chronic blockade of endothelin receptors in cirrhotic rats: hepatic and hemodynamic effects. Gastroenterology 1999; 116: 161–7.
93. Cho J J, Hocher B, Herbst H, Jia J D, Rubbl M, Hahn E G, et al. An oral endothelin-A receptor antagonist blocks collagen synthesis and deposition in advanced rat liver fibrosis. Gastroenterology 2000; 118: 1169–78.
94. Channick R N, Sitbon O, Barst R J, Manes A, Rubin L J. Endothelin receptor antagonists in pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43: 62–7S.
95. Sanyal A J. Angiotensin receptor blockade and portal hypertension: paradise gained, paradise lost. Gastroenterology 2001; 121: 487–90.
96. Schneider A W, Friedrich J, Klein C P. Effect of losartan, an angiotensin II receptor antagonist, on portal pressure in cirrhosis. Hepatology 1999; 29: 334–9.
97. Schepke M, Werner E, Bieker E, Schiedermaier P, Heller J, Neef M, et al. Hemodynamic effects of the angiotensin II receptor antagonist irbesartan in patients with cirrhosis and portal hypertension. Gastroenterology 2001; 121: 389–95.
98. Gonzalez-Abraldes J, Albillos A, Banares R, Del Arbol L R, Moitinho E, Rodriguez C, et al. Randomized comparison of long-term losartan versus propanolol in lowering portal pressure in cirrhosis. Gastroenterology 2001; 121: 382–8.
99. Debernardi-Venon W, Barletti C, Alessandria C, Marzano A, Baronio M, Todros L, et al. Efficacy of irbesartan, a receptor selective antagonist of angiotensin II, in reducing portal hypertension. Dig Dis Sci 2002; 47: 401–4.
100. Friedman S L. The answer: angiotensin II. The question: what do inflammation, oxidant stress and fibrogenesis have in common. J Hepatol 2004; 40: 1050–2.
101. Albillos A, Lledo J L, Banares R, Rossi I, Iborra J, Calleja J L, et al. Hemodynamic effects of alpha-adrenergic blockade with prazosin in cirrhotic patients with portal hypertension. Hepatology 1994; 20: 611–7.
102. Albillos A, Lledo J L, Rossi I, Perez-Paramo M, Tabuenca M J, Banares R, et al. Continuous prazosin administration in cirrhotic patients: effects on portal hemodynamics and on liver and renal function. Gastroenterology 1995; 109: 1257–65.
103. Albillos A, Garcia-Pagan J C, Iborra J, Bandi JC, Cacho G, Perez-Paramo M, et al. Propanolol plus prazosin compared with propanolol plus isosorbide-5-mononitrate in the treatment of portal hypertension. Gastroenterology 1998; 115: 116–23.
104. Frishman W H. Carvedilol. N Engl J Med 1998; 339: 1759–65.
105. Hemstreet B A. Evaluation of carvedilol for the treatment of portal hypertension. Pharmacotherapy 2004; 24: 94–104.
106. Bosch J, Kravetz D, Rodes J. Effects of somatostatin on hepatic and systemic hemodynamics in patients with cirrhosis of the liver: comparison with vasopressin. Gastroenterology 1981; 80: 518–25.
107. Reynaert H, Geerts A. Review article: pharmacological rationale for the use of somatostatin and analogues in portal hypertension. Aliment Pharmacol Ther 2003; 18: 375–86.
108. Reynaert H, Vaeyens F, Qin H, Hellemans K, Chatterjee N, Winand D, et al. Somatostatin suppresses endothelin-1-induced rat hepatic stellate cell contraction via somatostatin receptor subtype 1. Gastroenterology 2001; 121: 915–30.
109. Abraldes J G, Bosch J. Somatostatin and analogues in portal hypertension. Hepatology 2002; 35: 1305–12.
110. Nakabayashi H, Kurata Y, Usukura N, Takeda R. Somatostatin-sensitive neural system in the liver. Neurosci Lett 1986; 67: 78–81.
111. Nevens F. Review article: a critical comparison of drug therapies in currently used therapeutic strategies for variceal haemorrhage. Aliment Pharmacol Ther 2004; 20(Suppl. 3): 18–22.
112. Pilette C, Kirstetter P, Sogni P, Cailmail S, Moreau R, Lebrec D. Dose-dependent effects of a nitric oxide biosynthesis inhibitor on hyperdynamic circulation in two models of portal hypertension in conscious rats. J Gastroenterol Hepatol 1996; 11: 1–6.
113. Pizcueta P, Pique J M, Fernandez M, Bosch J, Rodes J, Whittle B J. Modulation of the hyperdynamic circulation of cirrhotic rats by nitric oxide inhibition. Gastroenterology 1992; 103: 1909–15.
114. Forrest E H, Jones A L, Dillon J F, Walker J, Hayes P C. The effect of nitric oxide synthase inhibition on portal pressure and azygos blood flow in patients with cirrhosis. J Hepatol 1995; 23: 254–8.